REMARKS

Rejection under 35 USC 103(a) in view of Chu et al., Giles et al., Drucker et al., Fang et al., and Topaly et al.

Claims 1, 15, 17-21, 25-32, 39-43, and 63-64 are rejected as being obvious in view of Chu et al., Giles et al., Drucker et al., Fang et al. and Topaly et al. This rejection is again respectfully traversed.

Chu et al., Giles et al., and Drucker et al. are relied on in the rejection for disclosures of using (-)-L-OddC or imatinib mesylate (STI-571) for the treatment of leukemia, and dosages for such agents in the treatment of leukemia.

Chu et al. (WO 96/07413) disclose the use of L-OddC for the treatment of cancer. See page 5, lines 17-27. The exemplified cancers include leukemia. See page 6, lines 18-28.

The article by Giles et al. discloses the results of a study in which patients with advanced leukemia were treated with troxacitabine (i.e., (-)-L-OddC). Of the 42 patients treated, 31 had acute myeloid leukemia (AML), 6 had myelodysplastic syndrome (MDS), 4 had acute lymphocytic leukemia (ALL), and 1 had chronic myeloid leukemia in blastic phase (CML-BP). The troxacitabine was administered in courses by continuous infusion for 30 minutes daily for 5 days with a starting dose of 0.72/m^2/day. In the study, 8 mg/m^2/day of troxatyl for 5 days was determined to be the MTD and the recommended dosage for further studies.

Giles et al. note that prior nucleoside compounds developed for cancer treatment, like Ara-C (cytarabine), were in the D-configuration, whereas troxacitabine has the L-configuration. See page 762. Additionally, Giles et al. disclose that the "pharmacokinetic behavior of troxacitabine is substantially different from that of other nucleoside analogs possessing a D configuration." See page 770, left column

Drucker et al. disclose the results of a study on STI571, a Bcr-Abl tyrosine kinase inhibitor. As noted by Drucker et al., Bcr-Abl is an enzyme that "is present in virtually all cases of chronic myeloid leukemia" and in 20% of acute lymphoblastic leukemia. The study investigated the treatment of patients with myeloid blast crisis and lymphoid blast crisis using STI571. The daily dosages ranged from 300 to 1000 mg. Drucker et al. state that the results

of the study demonstrates that STI571 "as a single" is well tolerated and has substantial activity. See page 1041 right column.

It is acknowledged in the rejection that these references do not disclose treating leukemia with a combination of (-)-L-OddC and STI571. In the rejection, it is argued that Chu et al. disclose using L-OddC in combination with other agents. It is further argued the applicants' specification acknowledges that STI571 has been used in combination with other agents. See discussion at page 3, lines 4-9 regarding studies involving STI571 in combination with cytarabine.

However, the cited prior art provides no suggestion that the combination of (-)-L-OddC and STI571 would be expected to achieve synergistic results. Conversely, as discussed further below, applicants' specification clearly demonstrates that the combination of (-)-L-OddC and STI-571 exhibits synergistic results.

With regards to synergy, the rejection relies on the disclosures of Fang et al. and Topaly et al. The Examiner argues that Fang et al. disclose that, in *in vitro* tests, co-treatment of certain cell lines with STI-571 and the agents Ara-C, etoposide and doxorubicin yielded increased apoptosis. See page 2252, right column. Additionally, it is argued that Topaly et al. disclose that, in *in vitro* tests, STI-571 exhibited synergism with respect to apoptosis induced by cytarabine (Ara-C), mafosfamide and etoposide.

Based on these disclosures, it is argued in the rejection that "the references provides one skilled in the art with the motivation and reasonable expectation of success in treating Bcr-Abl-positive CML with a combination thereby of STI-571 and other chemotherapeutic agents." However, the disclosures of the references do not establish the one skilled in the art would expect that one would achieve synergistic results, as opposed to merely additive, using a combination of STI-571 and any other anti-leukemia agent.

Nothing within these two disclosures suggests that STI-571 will interact synergistically with all other anti-leukemia agents, rather than having merely additive interaction or even an adverse interaction. Similarly, these two disclosures do not suggest that STI-571 will exhibit synergy with all other anti-leukemia agents, regardless of the mechanism of apoptosis induces by such agents.

The structures of cytarabine (Ara-C), etoposide, doxorubicin and mafosfamide are all clearly distinguishable from that of (-)-L-OddC. Of these four agents, only cytarabine has a

nucleoside structure. While (-)-L-OddC does possess a nucleoside-like structure, it has a dioxolane ring rather than a typical sugar ring and does not have the pendant hydroxy groups of the typical sugar ring, such as possessed by cytarabine. Furthermore, as noted above, (-)-L-OddC (troxacitabine) is recognized in the art as having a substantially different pharmacokinetic behavior than that of Ara-C. See the discussion above regarding the article by Giles et al.

In other words, Fang et al. and Topaly et al. references do not support a sweeping conclusion that synergism will be expected. One or ordinary skill in the art would not conclude or expect that, based on the limited *in vitro* studies on STI-571 in combination with 4 other agents, that STI-571 will exhibit synergistic effects when combined with any other anti-leukemia agent. Moreover, the disclosures of Fang et al. and Topaly et al. clearly would not lead one of ordinary skill in the art to expect that STI-571 will exhibit synergy with an anti-leukemia nucleoside agent having the L-configuration (rather than the D-configuration of Ara-C) and having a dioxolane structure, as in the case of (-)-L-OddC.

To further demonstrate that the premise of the rejection that synergy would be an expected result, applicants are filing herewith is a copy of the article Thiesing et al., "Efficacy of STI571, an Abl tyrosine kinase inhibitor, in conjunction with other antileukemia agents against Bcr-Abl-positive cells," Blood, Vol. 96, No. 9, (2000), pp. 3195-3199. The article by Thiesing describes the results of a study involving treatment of leukemia patients with STI571 in combination with other antileukemia agents, namely IFN (interferon-alpha), HU (hydroxyurea), DNR (daunorubicin), and Ara-C (cytosine arabinosine).

A conclusion of the study was that the addition of these other standard antileukemia agents, in most cases (3 out of 4), added to the antiproliferative activity of STI571 in the treatment of various stages of chronic myelogenus leukemia (CML). However, in the case of one of these 4 agents, i.e., HU, the result was actually antagonistic. See the "Discussion" section in the left hand column at page 3198.

In addition, for the three combinations that showed an increase in antiproliferative activity, only one of the combinations, namely Ara-C and STI571, showed a synergistic result, rather than merely an additive effect. See the isobolgrams of Figure 2. As explained in the right hand column of page 3197, in these isobolgrams a downward bowing curve is

indicative of a synergistic effect. Of the 4 isobolgrams in Figure 2, only the one for the Ara-C and STI571 showed a downward bowing curve, leading the authors to conclude:

> "...the combinations of STI571 plus IFN or DNR produced additive antileukemia effects, whereas ST1571 plus Ara-C produced the most substantial increase in inhibition of proliferation, consistent with a synergistic effect."

Thus, of the 4 types of combinations studied only one combination showed evidence of a synergistic effect, and another combination even showed evidence of an antagonistic effect. The other two combinations showed an additive effect, but not a synergistic effect. Thus, the results of this study clearly demonstrate that one of ordinary skill in the art **would not expect** that any given combination of ST1571 with an antileukemia agent will achieve a synergistic effect. Moreover, such a combination may even exhibit an antagonistic effect.

Applicants' specification clearly discloses that the combination of (-)-L-OddC and STI-571 exhibits synergistic results. The disclosures of Chu et al., Giles et al., Drucker et al., Fang et al. and Topaly et al. are devoid of any suggestion or expectation that combining (-)-L-OddC and STI-571 will achieve synergistic effects.

At pages 25-28 of the specification, applicants present the results of *in vivo* studies concerning the treatment of mice injected with KBM-5 and KBM-5R tumor cells. At the bottom of Table 1 (page 27), results are presented for Troxatyl alone at 10 mg/kg/day, Troxatyl alone at 25 mg/kg/day, STI-571 alone at 50 mg/kg/day, Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, and Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day (see schemes b)-f) at page 26).

As shown In Table 1, for Troxatyl alone at 10 mg/kg/day, the increased life span, ILS%, (mean survival time of treated animals minus that of control animals over the mean survival time of the control group) is 50.90% (ILS exceeding 25% indicates significant antitumor activity), and for STI-571 alone at 50 mg/kg/day, the ILS is 8.95%. However, when the animals were treated with Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, the ILS increased to **80.06**%.

Similarly, for Troxatyl alone at 25 mg/kg/day, ILS is 71.33%, and, as noted before, for STI-571 alone at 50 mg/kg/day, the ILS is 8.95%. However, when the animals were treated with Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day, the ILS increased to **125.17**%.

Additionally, again referring to the bottom of Table at page 27, none of the treatment schemes in which Troxatyl or STI-571 were administered alone showed any Long Term Survivors (LTS). Conversely, in the treatment scheme for Troxatyl at 10 mg/kg/day plus STI-571 at 50 mg/kg/day, there was 1 long term survivor, and in the treatment scheme for Troxatyl at 25 mg/kg/day plus STI-571 at 50 mg/kg/day, there was 3 long term survivors.

In view of the above remarks, it is respectfully submitted that of Chu et al., Giles et al., and Drucker et al., taken alone or in combination or further in combination with Fang et al. and/or Topaly et al., fail to render obvious applicants'' claimed invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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